REMARKS

Claims 1, 7, 8 and 10, as amended, appear in this amendment for the Examiner's active consideration. Claims 1, 7 and 8 have been amended to recite only the elected invention. Accordingly, claims 6, 9, 15, 18, 20 and 22 have been cancelled. Claims 7, 8 and 10 have been amended to depend from claim 1, instead of claim 6 which has been cancelled. The specification has been amended to correct informalities. As no new matter is introduced by these changes, the entry of these amendments is warranted at this time.

Claims 1, 6-10, 15, 22 and 31 are rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite. The Examiner alleges that the recitation of "antibody which has increased affinity for a fibroblast growth factor receptor" in claim 1 is indefinite. In response, claim 1 has been amended to specifically recite "antibody which blocks ligand-independent activation of fibroblast growth factor receptor 3 (FGFR3)," support for which is found in paragraph [0035] of the published application.

The Examiner also alleges that the recitation of "fibroblast growth factor receptor 3 (FGFR3)" in claim 1 is indefinite. Applicants respectfully disagree. As the binding of "structurally different" FGFR3 polypeptides by the same antibody is disclosed in Example 14, wherein both S249C and G380R mutations of FGFR3 were inhibited by an antibody of the present invention MSPRO59, it is clear that the breadth of the claim as originally recited is fully supported by the disclosure. However, in order to expedite the proceedings, Applicants have amended claim 1 to recite a specific FGFR3 amino acid sequence having an extracellular portion encoded by SEQ ID NO:4.

The Examiner further alleges that "constitutive activation" in claim 6 is indefinite. Since claim 6 has been cancelled, the rejection is rendered moot.

Based on the foregoing, the rejection under 35 U.S.C. 112, 2nd paragraph, is overcome and should be removed.

Claims 1, 6, 8-10, 15, 22 and 31 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the written description requirement. As claims 6, 9, 15 and 22 are cancelled, the rejection over these genes are rendered moot.

In response to the Examiner's reference to many different constitutively active FGFR3 mutations, Applicants respectfully point out that the specification provides ample descriptions for antibodies that are capable of blocking the function of FGFR3 receptors regardless of where

the mutation is located within the extracellular or transmembrane region of FGFR3. For example, as disclosed in Example 14, MSPRO59 inhibited both the FGFR3-S249C and FGFR3-G380R mutant polypeptides of the extracellular and the transmembrane regions of FGFR3, respectively. Furthermore, adequate description is also provided for the structure and function of antibodies targeted against the extracellular portion of FGFR3, which would block "distinct" FGFR3 polypeptides that are constitutively active (see Examples 8, 10, 12 and 14 of the published application).

Likewise, adequate disclosure is provided for the CDR regions of the antibody, such as in paragraph [0232] of the published application, in conjunction with the art-recognized role of CDR3 in governing antigen recognition. Therefore, one skilled in the art will readily envision the "members of the genus" of the present invention by combining the data of known CDR regions with that of the disclosed CDR3 regions of the present invention, especially in light of the guidance provided for CDR grafting in paragraphs [0148]-[0149] of the published application.

Nevertheless, in order to expedite the proceedings, Applicants have amended claim 1 to recite a specific FGFR3 having an extracellular portion which is encoded by SEQ ID NO:4 so as to further define the unique activity of the antibodies of the present invention. Therefore, the rejection under 35 U.S.C. § 112, first paragraph, as lacking adequate written description is overcome and should be withdrawn.

Claims 1, 6-10, 15, 22 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The present claims as amended are directed to antibodies that bind and block ligand-independent activation of a FGFR3 having an extracellular portion which is encoded by SEQ ID NO:4 (FGFR3-S371C, paragraph [0216] of the published application). As detailed in Examples 2 and 3, the specification provides step by step guidance for one skilled in the art to generate and verify antibodies against the FGFR3-S371C mutation. In particular, Example 2 discloses the generation of the FGFR3-S371C antigen and Example 3 recites the protocol for screening antibodies against the FGFR3-S371C antigen. In addition, Examples 6, 10 and 13 demonstrate both the in vivo and in vitro functions of molecules of the present invention. Thus, the specification provides sufficient guidance and direction to formulate antibodies of the present invention such that one skilled in the art can practice the present invention without undue experimentation. Therefore, the enablement requirement is fulfilled and

the rejection under 35 U.S.C. § 112, first paragraph, as lacking enabling disclosure should be withdrawn.

Claims 1, 6, 10, 15 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by International patent application publication No. WO 00/68424 to Cappellen et al. (referred to hereafter as "Cappellen"). Cappellen teaches methods of identifying FGFR3 mutations using PCR, RT-PCR or immunochemistry. While Cappellen teaches FGFR3 polypeptides including the FGFR3-IIIb and FGFR3-IIIc splice variants, the constitutively activating mutations R248C and S249C and potential generic inhibitors (including antibodies) specific to the extracellular region of the FGFR3-IIIb splice variant, it does not teach or suggest any antibodies that bind and block ligand-independent activation of a FGFR3 having an extracellular portion which is encoded by SEQ ID NO: 4, as recited in the present claims as amended. Therefore, the rejection over Cappellen is overcome and should be withdrawn.

Claims 1, 6, 10, 15 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by a publication by Johnston et al. (JBC, 270(51):30643-30650, 1995, referred to hereafter as "Johnston"), as evidenced by another publication by Chellaiah et al. (JBC, 274(49): 34785-34794, 1999, referred to hereafter as "Chellaiah"). Johnston teaches polyclonal FGFR3 antibodies raised against the second Ig-like extracellular domain (Ig II) of FGFR3 and specifically bind FGFR3 polypeptides that comprise this domain while Chellaiah shows that the Ig II extracellular domain of FGFR3 is required for FGF9 ligand binding specificity. However, Neither Johnston nor Chellaiah teaches or suggests that these polyclonal antibodies that bind and block ligand-independent activation of a FGFR3 having an extracellular portion which is encoded by SEQ ID NO: 4, as recited in the present claims as amended. Therefore, the rejection over Johnston as evidenced by Chellaiah is overcome and should be withdrawn.

Claims 1 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cappellen, in view of US Patent No. 5,843,450 to Dawson et al. (referred to hereafter as "Dawson"). As discussed above, Cappellen does not teach or suggest the present invention. Dawson teaches Hepatitis GB Virus (HGBV) synthetic peptides useful for a variety of diagnostic and therapeutic applications, as well as kits for using the HGBV nucleic acid or amino acid sequences and antibodies which specifically bind to HGBV. As explained above, Cappellen does not teach or suggest the present invention. Dawson does not remedy the deficiencies of Cappellen either since it does not teach or suggest any antibodies that bind and block ligand-

independent activation of a FGFR3 having an extracellular portion which is encoded by SEQ ID NO: 4, as recited in the present claims as amended. Thus, Cappellen and Dawson, either alone or in combination, do not teach or suggest the present invention. Therefore, the rejection over these two references should be withdrawn.

Claims 1 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston in view of Dawson. For the same reasons articulated for the combination of Cappellen and Dawson, the combination of Johnston and Dawson does not render claims 1 and 31 obvious and the rejection should be withdrawn.

It is understood that process claims 32-35 and 38-44 are currently withdrawn but they will be rejoined and allowed that when product claim 1 or composition claim 10, from which they depend, is allowed.

Accordingly, the entire application is now in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree with the Applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

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